General

Guideline Title

ACR Appropriateness Criteria® follow-up and retreatment of brain metastases.

Bibliographic Source(s)

Robbins JR, Elson A, Buatti JM, Chang EL, Cornelius RS, Estabrook NC, Germano IM, Ghafoori AP, Henderson MA, Shek-Man Lo S, Murad GJA, Robins HI, Siddiqui MS, Vassil AD, Videtic GMM, Yunes MJ, Gore EM, Expert Panel on Radiation Oncologyâ€“Brain Metastases. ACR Appropriateness CriteriaÂ® follow-up and retreatment of brain metastases [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 11 p. [38 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Patel SH, Robbins JR, Videtic GM, Gore EM, Bradley JD, Gaspar LE, Germano I, Ghafoori P, Henderson MA, Lutz ST, McDermott MW, Patchell RA, Robins HI, Vassil AD, Wippold FJ II, Expert Panel on Radiation Oncology-Brain Metastases. ACR Appropriateness Criteria® follow-up and retreatment of brain metastases. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 8 p. [33 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Follow-up and Retreatment of Brain Metastasis

Variant 1: 70-year-old man with non-small-cell lung cancer status post lobectomy 3 years ago with a single brain metastasis 6 months ago treated with radiosurgery. Now with new contralateral metastasis in nondominant temporal lobe measuring 2 cm. No extracranial disease present. Mild neurologic symptoms. KPS 80.

Treatment	Rating	Comments
Local Therapy Alone		
Surgical resection alone	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		
WBRT alone	6	Given 78-9 KPS, small metastasis, and toxicity of WBRT, SRS alone would be appropriate.

Treatment	Rating	Comments
Whole Brain Radiation Therapy (WBRT) Alone		
20 Gy/5 fractions	3	
30 Gy/10 fractions	7	
37.5 Gy/15 fractions	7	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	8	
Surgery and postop WBRT	7	Surgical intervention felt to be slightly less appropriate due to advanced age and previous response to SRS.
Surgery and postop SRS	3	SRS may be 1–5 fractions. There is limited evidence supporting this combination.
Chemotherapy Only	1	
Supportive Care	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: 60-year-old man with renal cancer history, status post-surgical resection of two cerebellar metastases and postoperative WBRT (35 Gy in 14 fractions) 18 months ago. Now with new 3 cm left frontal metastasis without edema. KPS is 90. No other signs of recurrence. No neurological symptoms.

Treatment	Rating	Comments
Local Therapy Alone		
Surgical resection alone	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
SRS alone	8	
Whole Brain Radiation Therapy (WBRT) Alone		
20 Gy/5 fractions	1	
25 Gy/10 fractions	1	
30 Gy/10 fractions	1	
37.5 Gy/15 fractions	1	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	1	
Surgery and postop WBRT	1	
Surgery and postop SRS	5	SRS may be 1–5 fractions. Use of this treatment depends on cavity size postoperatively. Given the size (which would limit SRS dose in radioresistant tumor) and the fact that resection alone can have higher rates of local recurrence than SRS alone, surgery and postoperative SRS may be appropriate. Additional consideration should be given for postoperative SRS if residual tumor is present in cavity.
Chemotherapy Only	1	
Supportive Care	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: 44-year-old woman with breast cancer (negative ER/PR, HER2/neu receptors) and multiple brain metastases 9 months ago, status post WBRT (30 Gy in 10 fractions). Now with recurrence of two asymptomatic well-separated bilateral anterior frontal masses, 1-2 cm in diameter each. No extracranial disease present. KPS 80.

Treatment	Rating	Comments
Local Therapy Alone		
Surgical resection alone	2	
SRS alone	9	
Whole Brain Radiation Therapy (WBRT) Alone		
20 Gy/5 fractions	1	
25 Gy/10 fractions	1	
30 Gy/10 fractions	1	
37.5 Gy/15 fractions	1	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	1	
Surgery and postop WBRT	1	
Surgery and postop SRS	2	SRS may be 1–5 fractions.
Chemotherapy Only	1	
Supportive Care	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: 49-year-old woman with melanoma, status post WBRT (30 Gy in 10 fractions) for multiple metastases 6 months ago. Now with recurrence of one 3.5 cm right parietal metastasis with edema causing weakness. No extracranial disease present. KPS 70.

Treatment	Rating	Comments
Local Therapy Alone		
Surgical resection alone	9	
SRS alone	5	
Whole Brain Radiation Therapy (WBRT) Alone		
20 Gy/5 fractions	1	
25 Gy/10 fractions	1	
30 Gy/10 fractions	1	
37.5 Gy/15 fractions	1	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	1	
Surgery and postop WBRT	1	
Surgery and postop SRS	3	SRS may be 1–5 fractions.
Chemotherapy Only	1	
Supportive Care	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: 73-year-old man with progressing metastatic lung cancer who was previously treated with whole brain radiation for multiple brain metastases 9 months earlier. Now with three new slightly symptomatic brain metastasis. KPS 50.

Radiologic Procedure	Rating	Comments
Local Therapy Alone		
Surgical resection alone	1	
SRS alone	2	Use of this treatment is size-dependent and also dependent on the patient's clinical response to steroids. SRS is generally not appropriate given low KPS and progressive systemic metastases.
Whole Brain Radiation Therapy (WBRT) Alone		
20 Gy/5 fractions	1	
25 Gy/10 fractions	2	
30 Gy/10 fractions	1	
37.5 Gy/15 fractions	1	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	1	
Surgery and postop WBRT	1	
Surgery and postop SRS	1	SRS may be 1–5 fractions.
Chemotherapy Alone	2	
Supportive Care	8	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 6: Follow-up after treatment of brain metastases. No extracranial disease present. KPS 90. Follow-up for 1–2 years.

Radiologic Procedure	Rating	Comments
Initial MRI head ≤3 months	8	
Subsequent MRI head every 3–6 months	8	
FDG-PET head only if MRI or CT abnormality suggests recurrence after radiosurgery or WBRT	5	Could consider this imaging modality to rule out possible tumor necrosis seen on MRI scans.
Subsequent MRI head when symptomatic on physical examination only	3	
Subsequent CT head every 4–6 months	2	
Subsequent FDG-PET head every 4–6 months	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Introduction/Background

Progress in the management of locally advanced and metastatic cancer has resulted in an increase in the number of patients diagnosed and living with brain metastases. Current estimates suggest that nearly 200,000 new patients develop brain metastases annually in the United States. It has

also been estimated that up to 40% of patients with cancer will develop brain metastases. Hence, although progress has been made in decreasing the incidence of lung cancer deaths (largely due to fewer smokers) and prolonging survival in other systemic cancers such as breast and colorectal, the incidence of brain metastases continues to increase as patients with metastatic disease live longer.

The most common source of brain metastases is lung cancer. A recent report on 177 patients with surgically staged IIIA non-small-cell lung cancer (NSCLC) found that 34% of them had cancer recur in the brain as the first site of failure, and that 40% developed brain metastases at some point in their course. In the past, brain metastases were thought to herald the onset of a rapidly fatal course in patients with cancer due to the limited efficacy of systemic therapies and whole brain radiation therapy (WBRT) (median survival 4 to 7 months; 2-year survival ≤10%). Survival rates for patients with brain metastases become significant only when extracranial disease is controlled.

Reports are emerging, however, describing long-term survivorship on the order of multiple years after treatment of brain metastasis. Several single and multi-institutional retrospective reviews revealed 2.5% to 6% 5-year overall survival after treatment of brain metastases with some patients living longer than 10 years. As expected, patients with initially higher Karnofsky performance status (KPS), fewer brain metastases, and limited extracranial disease experienced longer survival. In addition, a recent phase III trial of 359 patients randomized to local therapy alone for one to three brain metastases followed by observation or WBRT reported >20% survival at 2 years. Thus, as a growing percentage of treated patients may live long enough to experience relapse again in the brain, there is a greater need for appropriate follow-up and management of recurrent brain metastases.

Retreatment for brain metastases may be required following a variety of initial treatments such as WBRT, surgery, radiosurgery, chemotherapy, and combinations of these. The choice of treatment modality after recurrence will depend on the size, number, timing, and location of the recurrent metastases, the patient's performance status, extracranial disease control, and prior treatment of the intracranial disease. There appears to be an increasing number of patients who have received only surgery or radiosurgery as their initial management of brain metastases. This trend is likely driven by the increasing availability of stereotactic radiosurgery (SRS) and improvements in neuroimaging and surgical techniques. For the purpose of general review, these guidelines do not elaborate on the unique aspects of small-cell/neuroendocrine lung cancer due to its high propensity of brain metastasis and patients receiving prophylactic cranial irradiation as part of their upfront treatment.

Whole Brain Radiation Therapy

Historically, WBRT has been a fundamental part of the initial treatment of brain metastases, but due to the increasing use of local therapy alone initially for selected patients with brain metastases, WBRT is often being used in the salvage setting. Two large randomized trials involving initial local therapy followed by observation reported on the use of WBRT after failure in 16% and 31% of patients in the observation arms (see Variant 1 above). In patients who initially received WBRT, repeat WBRT has not been routinely administered for retreatment, primarily due to concerns about severe neurotoxicity. However, one institution reviewed 72 patients who underwent two courses of WBRT for brain metastases. The most common initial fractionation scheme was 20 Gy in 5 fractions, whereas the most frequent reirradiation schedule was 25 Gy in 10 fractions. The median survival time after reirradiation was 4.1 months. Performance status (Eastern Cooperative Oncology Group criteria), neurological function class (Radiation Therapy Oncology Group classification), and documented response to reirradiation were predictive of survival times.

Another review of 31 patients undergoing repeat WBRT with the most common first and second course being 30 Gy in 10 fractions revealed a median survival after reirradiation of 4 months with 68% symptomatic improvement after treatment. Grade ≥2 encephalopathy or cognitive disturbance was noted in 32% of patients after reirradiation with 74% of patients having magnetic resonance imaging (MRI) findings suggestive of brain atrophy after reirradiation, which highlights the concern of neurologic deterioration in this setting. These studies suggest that there may be a role for WBRT for the retreatment of progressive brain metastases after prior WBRT.

Radiosurgery

Radiosurgery for recurrent brain metastases is a viable option if size and number permit, and has been described in the setting of prior surgery, radiosurgery, and WBRT. In addition, this modality is becoming increasingly available at many centers. In patients undergoing radiosurgery for recurrence following initial WBRT, two studies reported 1-year and 2-year local control rates of 68% to 74% and 58%, respectively. Another study reported a 91% response rate of treated lesions with acute grade 2 toxicity requiring steroids in 16% of patients and an eventual radionecrosis rate of 6%. Good local control, as high as 90%, has been reported in patients who underwent repeat SRS to previously treated or newly developed sites, but risk for radiation necrosis increased with repeat treatments to the same areas. Favorable prognostic factors for survival after SRS for recurrent brain metastases included age <50, KPS >60, and longer interval between WBRT and SRS. Recently there has been a trend to use radiosurgery in the setting of adjuvant therapy to the tumor bed after surgical resection as part of initial therapy of brain metastases, but only one report evaluated this scheme in the recurrent setting after prior WBRT. In their retrospective cohort of 79 patients, the local control rate was 94.9% with a symptomatic radionecrosis rate of only 3.8%. Similarly, studies in the setting of the initial treatment of brain metastases suggest that the resection cavity can be treated effectively with 1 to 5 fractions of stereotactic radiation therapy. Together these data suggest that SRS is one valid approach in managing those patients having brain relapses alone or in combination with other modalities even after prior therapies

including WBRT and especially if limited new foci are present (see Variant 2 and Variant 3 above).

Surgery

Surgery may be indicated for palliation of mass effect from progressive or hemorrhagic brain metastases and may also be an important diagnosis and management tool in determining the nature of a progressive lesion after radiation treatment. Factors to consider regarding the use of surgical resection after prior irradiation include clinical or radiographic evidence of a progressive lesion, KPS >60, and stable or absent extracranial disease. One author reported local control rates range from 69% to 79%, and one retrospective study comparing resection to no resection showed a modest survival benefit (see Variant 4 above).

Chemotherapy

Chemotherapy has occasionally been a successful strategy for chemosensitive tumors. Some evidence suggests that some chemotherapy and biological treatments may be effective in brain metastases. These studies are mostly based on smaller experiences using various agents. Temozolomide, capecitabine, and gefitinib have also been reported to be used in treating brain metastases from melanoma, breast cancer, and lung cancer, respectively. A phase II study of salvage chemotherapy using dose-dense temozolomide in 157 patients with brain metastases not amenable to surgery or radiosurgery revealed a 26% control rate defined as complete or partial response or stable disease. Response of brain metastases to antiepidermal growth factor inhibitors such as gefitinib or erlotinib provides some new alternatives for the management of brain metastases. These targeted agents may be particularly attractive for patients with less symptomatic, smaller recurrent brain metastases. Dual tyrosine kinase inhibitors (e.g., lapatinib) have recently been shown to benefit some HER2/neu-positive breast cancer patients and also those with recurrent brain metastases.

Although chemotherapy has been traditionally believed to have poor central nervous system penetrance and therefore poor efficacy in brain metastases, a recent prospective phase II trial evaluating 43 patients with brain metastases from NSCLC treated initially with pemetrexed and cisplatin followed by delayed WBRT, as well as a pilot study of 48 patients with brain metastases from NSCLC randomized to up front WBRT versus WBRT after chemotherapy revealed intracerebral response rates of 41% and 28%, respectively, in the chemotherapy upfront setting.

Supportive Care

Best supportive care (BSC) is always an option for select patients with recurrent brain metastases. Factors important in evaluating prognosis in these patients include, but are not limited to, performance status, status of extracranial disease, number of brain metastases, and age. Patients with a poorer prognosis may be better served with an earlier discussion of BSC considering their reduced survival rates. Some data suggest that BSC is an appropriate option in select patients. A group of researchers conducted a matched pair analysis of 113 patients with brain metastases treated with BSC alone matched to a similar group of patients treated with WBRT. They observed no survival difference, but overall survival was limited in both groups (median overall survival 2 months). In addition, the interim data from an ongoing randomized phase III noninferiority trial comparing quality-adjusted life years after optimal supportive care (OSC) or OSC + WBRT in NSCLC patients with inoperable brain metastases suggests that there is no evidence of inferior quality of life or overall survival for patients managed by OSC alone (see Variant 5 above). Given that these studies pertain to patients managed with BSC in the initial setting, this strategy may be even more appropriate in the recurrent setting, when previous treatment modalities have already been employed.

Follow-up of Brain Metastases

After the treatment of brain metastasis, determining the proper timing and modality of follow-up imaging and distinguishing treatment response from recurrence are major management considerations. This issue is complicated by the lack of reliable early indicators of response versus progression. One study reported a median time of 8.8 months to new metastasis after initial SRS. The authors recommended close surveillance with a 3-month interval between MRI in order to identify new metastasis early in order to facilitate the most effective treatment. Additionally, another group performed 3-month interval MRI scans in their study of local therapy with or without WBRT and recommended that when WBRT is withheld, close serial imaging follow-up should be performed to identify early asymptomatic brain recurrences. Although the optimal timing and method of radiographic follow-up of treated brain metastases is the subject of some debate, MRI has become the preferred imaging modality, especially given its wide availability and the development of newer applications such as spectroscopy and diffusion and perfusion-weighted imaging. Given the costs associated with serial MR imaging, decisions regarding its use should take into account the individual patient situation and the likelihood of gaining useful information that may influence management decisions.

A common difficulty encountered during the radiographic follow-up of treated brain metastases is differentiating tumor recurrence or progression from radiation effect. This is particularly vexing in asymptomatic patients with high performance status. Although invasive pathological evaluation remains the only definitive test to make this distinction, it is not always practical or feasible, and some cases of radiation necrosis can be managed nonsurgically. For this reason, several imaging modalities including standard and advanced MRI sequences, MR spectroscopy, perfusion computed tomography (PCT), and fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) and methionine positron emission tomography (PET) have

been investigated to differentiate between these entities. Two studies showed that FDG-PET as well as C-11 methionine PET imaging is effective in detecting tumor recurrence compared to radiation changes in patients with suspected recurrent lesions. PCT has been evaluated in a recent prospective trial of 20 patients previously treated with radiosurgery and normalized cerebral blood volume had a sensitivity of 86% and specificity of 100% for identification of radiation necrosis compared to for suspected recurrence. A study of 68 patients who underwent surgical resection after previous SRS for brain metastases due to suspected lesion progression showed that lack of correspondence between T1 contrast-enhanced volume and the T2 hypointense lesion margin (T1/T2 mismatch) on standard MR sequencing was significantly associated with radiation effect as opposed to tumor progression with a sensitivity and specificity of 83% and 91%. Advanced MRI sequences including dynamic susceptibility-weighted contrast-enhanced MRI-produced metrics such as relative cerebral blood volume have been used to assess the microvascularity and permeability of brain tissue and have shown the ability to distinguish between necrosis and recurrence with high sensitivity and specificity in patients with suspected or pathologically confirmed tumor recurrence. These findings suggest that examination of cerebral blood volume ratios can predict for tumor recurrence. Further research in this arena will likely contribute to better determination of imaging changes after radiation treatments. When recurrence of brain metastases is confirmed, surgery, radiosurgery, or WBRT may be considered to achieve disease control (see Variant 5 above). In addition to serial imaging, clinical assessment and toxicity management for patients treated for brain metastases are paramount, as delayed complications have been reported for patients as many as 10 years after treatment (see Variant 5 above).

Summary of Recommendations

The issues regarding postirradiation management and retreatment of brain metastases revolve around several concerns:

- The need to assess the effects of and manage sequelae of treatment.
- The need for appropriate surveillance and the ability to accurately distinguish late treatment effects from recurrence, so that further treatment can be administered as appropriately as possible.
- The goal of detecting recurrences prior to the onset of symptoms, when patients may best tolerate additional treatment, and when lesion size does not result in symptomatology or preclude the use of radiosurgery.
- The need to determine the most appropriate among the various management options based on patient characteristics and preferences, previous treatments employed, and potential risks and toxicities of treatment.

Abbreviations

- CT, computed tomography
- ER, estrogen receptor
- FDG-PET, fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography
- HER2, human epidermal growth factor receptor 2
- KPS, Karnofsky performance status
- MRI, magnetic resonance imaging
- PR, progesterone receptor
- SRS, stereotactic radiosurgery
- WBRT, whole brain radiation therapy

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

Brain metastases with cancer (e.g., lung, breast, colorectal)

Guideline Category

Evaluation

Treatment

Clinical Specialty

Neurological Surgery

Neurology

Oncology

Radiation Oncology

Radiology

Intended Users

Health Plans

Hospitals

Managed Care Organizations

Physicians

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of various radiologic procedures for the treatment and retreatment of patients with brain metastases

Target Population

Patients requiring follow-up and retreatment of brain metastases

Interventions and Practices Considered

1. Local therapy alone
    - Surgical resection
    - Stereotactic radiosurgery (SRS)
2. Whole brain radiation therapy (WBRT) alone
3. Combined therapy
    - WBRT and SRS
    - Surgery and postoperative WBRT
    - Surgery and postoperative radiosurgery
4. Chemotherapy alone
5. Supportive care
6. Follow-up
    - Magnetic resonance imaging (MRI), head (initial and subsequent)
    - Computed tomography (CT), head
    - Fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), head

Major Outcomes Considered

- Local control rates

- Median survival time
- Survival rates
- Duration of response
- Treatment failure
- Adverse effects of treatment
- Utility of imaging procedures for follow-up of brain metastases

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Summary

Of the 33 citations in the original bibliography, 18 were retained in the final document. Articles were removed from the original bibliography if they were more than 10 years old and did not contribute to the evidence or they were no longer cited in the revised narrative text.

A new literature search was conducted in August 2013 to identify additional evidence published since the *ACR Appropriateness Criteria® Follow-up and Retreatment of Brain Metastases* topic was finalized. Using the search strategy described in the literature search companion (see the "Availability of Companion Documents" field), 170 articles were found. Six articles were added to the bibliography. One hundred sixty-four articles were not used due to either poor study design, the articles were not relevant or generalizable to the topic, the results were unclear, misinterpreted, or biased, or the articles were already cited in the original bibliography.

The author added 14 citations from bibliographies, Web sites, or books that were not found in the new literature search.

See also the American College of Radiology (ACR) Appropriateness Criteria® literature search process document (see the "Availability of Companion Documents" field) for further information.

Number of Source Documents

Of the 33 citations in the original bibliography, 18 were retained in the final document. The new literature search conducted in August 2013 identified six articles that were added to the bibliography. The author added 14 citations from bibliographies, Web sites, or books that were not found in the new literature search.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Study Quality Category Definitions

Category 1 - The study is well-designed and accounts for common biases.

Category 2 - The study is moderately well-designed and accounts for most common biases.

Category 3 - There are important study design limitations.

Category 4 - The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

a. The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description).
b. The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence.
c. The study is an expert opinion or consensus document.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author assesses the literature then drafts or revises the narrative summarizing the evidence found in the literature. American College of Radiology (ACR) staff drafts an evidence table based on the analysis of the selected literature. These tables rate the study quality for each article included in the narrative.

The expert panel reviews the narrative, evidence table and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the variant table(s). Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development documents (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The American College of Radiology (ACR) Appropriateness Criteria (AC) methodology is based on the RAND Appropriateness Method. The appropriateness ratings for each of the procedures or treatments included in the AC topics are determined using a modified Delphi method. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. The expert panel members review the evidence presented and assess the risks or harms of doing the procedure balanced with the benefits of performing the procedure. The direct or indirect costs of a procedure are not considered as a risk or harm when determining appropriateness. When the evidence for a specific topic and variant is uncertain or incomplete, expert opinion may supplement the available evidence or may be the sole source for assessing the appropriateness.

The appropriateness is represented on an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate" where the harms of doing the procedure outweigh the benefits; and 7, 8, or 9 are in the category "usually appropriate" where the benefits of doing a procedure outweigh the harms or risks. The middle category, designated "may be appropriate," is represented by 4, 5, or 6 on the scale. The middle category is when the risks and benefits are equivocal or unclear, the dispersion of the individual ratings from the group median rating is too large (i.e., disagreement), the evidence is contradictory or unclear, or there are special circumstances or subpopulations which could influence the risks or benefits that are embedded in the variant.

The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating. To determine the panel's recommendation, the rating category that contains the median group rating without disagreement is selected. This may be determined after either the first or second rating round. If there is disagreement after the second

rating round, the recommendation is "may be appropriate."

This modified Delphi method enables each panelist to articulate his or her individual interpretations of the evidence or expert opinion without excessive influence from fellow panelists in a simple, standardized and economical process. For additional information on the ratings process see the Rating Round Information document on the ACR Web site.

Additional methodology documents, including a more detailed explanation of the complete topic development process and all ACR AC topics can be found on the ACR Web site (see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current literature and expert panel consensus.

Summary of Evidence

Of the 38 references cited in the *ACR Appropriateness Criteria® Follow-up and Retreatment of Brain Metastases* document, 32 are categorized as therapeutic references including 8 well-designed studies and 19 good quality studies. Additionally, 6 references are categorized as diagnostic references including 1 good quality study, and 4 quality studies that may have design limitations. There are 6 references that may not be useful as primary evidence.

Most of the references are well-designed or good quality studies and provide good evidence.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Selection of appropriate procedures for follow-up and retreatment of patients with brain metastasis

Potential Harms

- Repeat whole brain radiation therapy (WBRT) has not been routinely administered for retreatment after previous WBRT, primarily due to

concerns about severe neurotoxicity. One study showed grade ≥2 encephalopathy or cognitive disturbance in 32% of patients after reirradiation with 74% of patients having magnetic resonance imaging (MRI) findings suggestive of brain atrophy after reirradiation, which highlights the concern of neurologic deterioration in this setting.

- In patients who underwent repeat stereotactic radiosurgery (SRS), risk for radiation necrosis increased with repeat treatments to the same areas.
- A common difficulty encountered during the radiographic follow-up of treated brain metastases is differentiating tumor recurrence or progression from radiation effect.
- Clinical assessment and toxicity management for patients treated for brain metastases are paramount, as delayed complications have been reported for patients as many as 10 years after treatment.

Qualifying Statements

Qualifying Statements

The American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Bibliographic Source(s)

Robbins JR, Elson A, Buatti JM, Chang EL, Cornelius RS, Estabrook NC, Germano IM, Ghafoori AP, Henderson MA, Shek-Man Lo S, Murad GJA, Robins HI, Siddiqui MS, Vassil AD, Videtic GMM, Yunes MJ, Gore EM, Expert Panel on Radiation Oncologyâ€“Brain Metastases. ACR Appropriateness CriteriaÂ® follow-up and retreatment of brain metastases [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 11 p. [38 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1999 (revised 2014)

Guideline Developer(s)

American College of Radiology - Medical Specialty Society

Source(s) of Funding

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology-Brain Metastases

Composition of Group That Authored the Guideline

Panel Members: Jared R. Robbins, MD (*Principal Author*); Andrew Elson, MD (*Research Author*); John M. Buatti, MD; Eric L. Chang, MD; Rebecca S. Cornelius, MD; Neil C. Estabrook, MD; Isabelle M. Germano, MD; A. Paiman Ghafoori, MD; Mark A. Henderson, MD; Simon Shek-Man Lo, MB, ChB; Gregory J. A. Murad, MD; H. Ian Robins, MD, PhD; M. Salim Siddiqui, MD, PhD; Andrew D. Vassil, MD; Gregory M. M. Videtic, MD; Michael J. Yunes, MD; Elizabeth M. Gore, MD (*Panel Chair*)

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Patel SH, Robbins JR, Videtic GM, Gore EM, Bradley JD, Gaspar LE, Germano I, Ghafoori P, Henderson MA, Lutz ST, McDermott MW, Patchell RA, Robins HI, Vassil AD, Wippold FJ II, Expert Panel on Radiation Oncology-Brain Metastases. ACR Appropriateness Criteria® follow-up and retreatment of brain metastases. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 8 p. [33 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the American College of Radiology (ACR) Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2015 Feb. 3 p. Electronic copies: Available from the American College of Radiology (ACR) Web site.
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2015 Feb. 1 p. Electronic copies: Available from the ACR Web site.
- ACR Appropriateness Criteria®. Evidence table development – diagnostic studies. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available from the ACR Web site.
- ACR Appropriateness Criteria®. Evidence table development – therapeutic studies. Reston (VA): American College of Radiology; 2013 Nov. 4 p. Electronic copies: Available from the ACR Web site.
- ACR Appropriateness Criteria® follow-up and retreatment of brain metastases. Evidence table. Reston (VA): American College of Radiology; 2014. 17 p. Electronic copies: Available from the ACR Web site.
- ACR Appropriateness Criteria® follow-up and retreatment of brain metastases. Literature search. Reston (VA): American College of Radiology; 2014. 1 p. Electronic copies: Available from the ACR Web site.

Patient Resources

None available

NGC Status

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